BMPs direct sensory interneuron identity in the developing spinal cord using signal-specific not morphogenic activities.

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Authors: Madeline G Andrews, Lorenzo M Del Castillo, Eliana Ochoa-Bolton, Ken Yamauchi, Jan Smogorzewski, Samantha J Butler

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Public Summary:
Spinal neurons are generated during embryonic development, when instructive molecules called growth factors tell immature cells – called neural progenitors - to become motor or sensory neurons. My laboratory has been studying one family of such growth factors called the Bone Morphogenetic Proteins or BMPs. My interest has focused on the observation that they are present in a very specific region of the developing spinal cord – a cluster of cells called the roof plate, found at the back of the spinal cord. Work from many laboratories has suggested that the BMPs act from the roof plate to direct the adjacent cells to become different types of sensory neurons. However, it was unclear how this mechanism worked. One model suggested that the BMPs act as morphogens, meaning that the BMPs have different activities depending on their concentration. In the spinal cord, the BMPs have been proposed to act as a morphogen gradient from the roof plate. Thus, the neural progenitor cells closest to the roof plate are exposed to a high concentration of BMPs, and thereby become one type of sensory neuron. In contrast, the neural progenitors arising further away from the roof plate are exposed to lower concentrations of BMPs and accordingly form another type of sensory relay neuron. While this model makes sense for other growth factors in different regions of the nervous system, a peculiarity of the dorsal spinal cord is that there are many different types of BMPs present in the roof plate. Thus, another explanation was that each BMPs has a distinct “signal specific” activity– that can direct neural progenitor cells towards a specific type of sensory neuron. We tested these models, by manipulating the concentration of different types of BMPs in chicken embryonic spinal cords and by applying different concentrations of BMPs to mouse embryonic stem cells. We found no evidence that the BMPs work like morphogens. Rather, each BMP always produced a range of specific types of sensory neurons, regardless of the concentration of the BMP. Increasing the concentration of a specific BMP made more of those neurons, but did not produce a different range of sensory neuron. The observation that each BMP has its own specific range of activities directing cell fate in the spinal cord strongly supported the “signal specific” model.

Scientific Abstract:
The Bone Morphogenetic Protein (BMP) family reiteratively signals to direct disparate cellular fates throughout embryogenesis. In the developing dorsal spinal cord, multiple BMPs are required to specify sensory interneurons (INs). Previous studies suggested that the BMPs act as concentration-dependent morphogens to direct IN identity, analogous to the manner in which sonic hedgehog patterns the ventral spinal cord. However, it remains unresolved how multiple BMPs would cooperate to establish a unified morphogen gradient. Our studies support an alternative model: BMPs have signal-specific activities directing particular IN fates. Using chicken and mouse models, we show that the identity, not concentration, of the BMP ligand directs distinct dorsal identities. Individual BMPs promote progenitor patterning or neuronal differentiation by their activation of different type I BMP receptors and distinct modulations of the cell cycle. Together, this study shows that a 'mix and match' code of BMP signaling results in distinct classes of sensory INs.